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Novel Measures of Volume Status and Cardiac Function in Traumatic Shock

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14. ABSTRACT

The purpose of this study was (1) to identify better markers of volume status and the adequacy of resuscitation in patients with traumatic shock and (2) to determine the incidence, time course, and clinical relevance of trauma-associated cardiac dysfunction. To achieve these aims, we evaluated a panel of cardiac biomarkers of cardiac function and the focused rapid echocardiographic evaluation serially over time in a civilian model of military trauma. Upon closure of the study, only six patients were enrolled, so no association between biomarkers and outcome could be determined. However, the study found that the majority of severely injured trauma patients have cardiac dysfunction during the initial 24 hours and periodically over 10 days. Furthermore, echo proved to be a safe method to assess volume status and cardiac function. These pilot data suggest that further study of biomarkers and echocardiography in trauma patients is warranted.

15. SUBJECT TERMS
Focused cardiac ultrasound, biomarkers in trauma, FREE, point-of-care ultrasound

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1.0 SUMMARY

The purpose of this study was to identify better markers of volume status and to determine the incidence, time course, and clinical relevance of trauma-associated cardiac dysfunction in patients with traumatic shock. This was a prospective observational study in critically injured trauma patients. Patients who met criteria for traumatic shock were enrolled. Blood was sampled at time point 0 and every 6 hours for 72 hours and then daily for 10 days. Serial focused rapid echocardiographic evaluation exams were performed at the same study points. In addition, clinical data were recorded, including fluid balance and the need for operative intervention. Over a 12-month study period, six patients were enrolled. The inclusion criteria resulted in a reasonable model for military trauma patients in a high-volume civilian trauma center. The patients were 20-49 years old, with five of six being 30 years of age or younger. Despite the small numbers, several interesting trends were identified. Four of six (66%) patients were found to have a mildly depressed ejection fraction (50-55%) early in the treatment period. The trend of both the serial echocardiograms and the biomarkers suggests that cardiac dysfunction develops early, within 6 hours of admission, and is followed by evidence of endothelial damage (adrenomedullin) from days 2-4 and renal injury (neutrophil gelatinase-associated lipocalin) from days 7-8. No definitive conclusions can be drawn from this small study. However, these pilot data bring to light some interesting observations about early cardiac dysfunction, subsequent endothelial damage, and renal dysfunction.

2.0 INTRODUCTION

Early, aggressive fluid resuscitation in shock is associated with improvement in outcomes including mortality in both traumatic and septic shock [1-4]. On the other hand, a clear association between cumulative fluid balance and mortality exists [5-7]. There are costs to both over- and under-resuscitation. Better direct measures of intravascular and intra-cardiac volume are urgently needed to guide fluid administration prior to and during transport. In addition, there is no portable, robust method of assessing cardiac function and output. The focused rapid echocardiographic evaluation (FREE) was developed to provide information about cardiac function and volume assessment and is in routine use for evaluation of intensive care unit patients at the Shock Trauma Center in Baltimore, MD [8-11].

Point-of-care ultrasound is rapid, portable, and becoming increasingly important in trauma management. More sophisticated and quantitative echocardiography, like the FREE, can diagnose cardiac dysfunction and provide valuable information about volume status. At the same time, serum biomarkers could provide additional information on cardiac inflammation and volume status. We planned to assess a panel of biomarkers and the FREE over the entire course of resuscitation in critically ill trauma patients. The biomarkers assessed included measures of cardiac muscle damage: high sensitivity cardiac troponin I (HS TNI), B-type natriuretic peptide (BNP), mid-regional pro-atrial natriuretic peptide (ANP), neutrophil gelatinase-associated lipocalin (NGAL), procalcitonin (PCT), and mid-regional pro-adrenomedullin (ADM).

3.0 BACKGROUND

At present, clinicians have no effective way of determining patients' volume status during resuscitation either in the field or in a fixed facility. Better direct measures of intravascular and intra-cardiac volume are needed to guide fluid administration. Pulmonary artery catheters (PACs) are highly invasive and inappropriate for field use. Furthermore, PACs and central venous pressure have both been shown to be inaccurate and not beneficial to patients in shock [12-14]. In addition, the incidence, time course, and etiology of cardiac dysfunction in trauma patients are poorly understood. A complicating factor is that fluid status and cardiac function are likely intertwined: over- or under-resuscitation may play some role in the development of post-traumatic cardiac dysfunction. Conversely, fluid management must be adjusted in patients with dysfunction, but rarely can be done by other than purely empirical means in other than highly specialized clinical settings.

In the civilian and non-trauma settings, the documentation and assessment of acute cardiac muscle injury by biomarker assays have been an established procedure for more than 40 years, and the newer assays—HS TNI, BNP, ANP, NGAL, PCT, and ADM—have improved the sensitivity, specificity, and timeliness of this approach [15,16]. De'Ath and colleagues have shown both BNP and TNI to be elevated in trauma without evidence of chest trauma, or known coronary disease, and those elevations are associated with an increase in risk of adverse coronary events and death [17,18]. Our center has developed the FREE, which is an abbreviated and protocolized form of comprehensive transthoracic echocardiogram suitable for use by non-specialists and mid-level practitioners. The FREE measures volume responsiveness and cardiac output, as well as several other physiologic parameters, generates treatment recommendations, and has demonstrated utility in fluid management of trauma patients in the intensive care unit (ICU) [8,9]. This study sought to combine these metrics to gain better understanding of the time course and possibly the etiology of trauma-induced cardiac dysfunction.

4.0 METHODS

This was single-center, 12-month observational study using a convenience sample of patients requiring resuscitation in our Level 1 civilian trauma center. After securing approval for this study protocol from the University of Maryland School of Medicine and U.S. Air Force Institutional Review Boards, enrollment was initiated.

The diagnosis of shock and eligibility for this study were determined at 6 hours after admission. To be eligible, patients had to be expected to survive more than 24 hours, have a clinical plan for ICU admission, have a clinical plan for a phlebotomy every 6 hours, and have one or more of the following: heart rate >120 bpm, systolic blood pressure <90 mmHg, or ≥1 unit packed red blood cells transfused.

All patients underwent a full-FREE within 12 hours of admission and then daily for 10 days. Efforts were made to secure this first assessment within 2 hours of enrollment. Full-FREE measurements include left ventricular ejection fraction (LVEF), diastolic dysfunction (graded 1-3), right ventricular (RV) dysfunction (mild-moderate-severe), left ventricular internal dimension at end diastole (LVIDd), inferior vena cava (IVC) diameter, change in IVC diameter with respiration (Δ IVC), and stroke volume variation with respiration. A short-FREE was performed every 6 hours for the first 72 hours. Short-FREE measurements include volume measurements, ejection fraction (EF), and an assessment of RV function.

Blood samples were processed from admission, every 6 hours for the first 72 hours, then daily for 10 days. As part of routine ICU care, blood is drawn on admission, every 5 hours for the first 72 hours, and daily while the patient is in the ICU. Every effort was made to use remnant blood whenever possible. Blood was processed for HS TNI, BNP, ANP, NGAL, PCT, and ADM.

Data on resuscitation during the initial 72 hours were recorded, including amount of fluid administered, blood transfusions, surgeries and other invasive procedures, and estimated blood loss. In addition, we recorded measures of cellular perfusion, including base deficit and serum lactate, drawn at the time of the biomarkers. Outcome variables include hospital mortality, ventilator-free days, development of adult respiratory distress syndrome, renal dysfunction, and renal failure as measured by serum chemistries and need for dialysis.

4.1 Ultrasound Examinations

All ultrasound exams were performed with one of two portable ultrasound systems, the CX 50® (Phillips Healthcare, Andover, MA) or the Vivid i® (GE Healthcare, Waukesha ,WI). The patients were given a study number, and all research images were linked only to that number. Stored images from the machines were downloaded to the ProSolv® Cardiovascular DICOM Imaging Storage System (FUJIFILM Medical Systems, Stamford, CT) on a protected server. The ProSolv system was used to interpret the images and store the reports linked to the de-identified study number. Study staff ensured that performance of the exam in no way interfered with patient care. Studies were only performed if the exam could be done without delaying care or otherwise impacting the patient's course. If potentially important clinical information was revealed by the FREE exam (i.e., low EF), this information was given to the clinical team. The machines are small and portable, and our various clinical teams are very familiar with the practice in our ICU and the management of the severely injured.

Several assessments and measurements are made as part of the FREE. The primary measures of volume status are the LVIDd, inferior vena cava diameter (IVCd), and Δ IVC. The functional measurements include assessments of relaxation or diastolic function. The LVEF is determined by careful visual inspection of the left ventricle (LV) in all four of the standard windows. RV function is also determined by careful visual assessment.

4.2 Statistical Analysis

Due to the late start and early closure of this study, no comparative statistics or regression analysis was performed. Averages are expressed as percentages and ± standard deviation when appropriate.

5.0 RESULTS

Over a 12-month period, six patients were enrolled. Five out of the six were enrolled from March-June as a result of the expected spring and summer increase in young civilian trauma. The inclusion criteria resulted in a reasonable model for military trauma patients in a high-volume civilian trauma center. The patients were 20-49 years old, with five out of six being 30 years of age or younger. In addition, they sustained a combination of severe blunt and penetrating trauma injuries, similar to those that could be acquired in combat. Furthermore, five

of six required surgery, including cardiac surgery and various orthopedic operations. The study proved to be feasible in design, as serial FREEs were obtained in 106 of 123 time points (88%) and blood draws were obtained in 118 of 123 time points (96%).

5.1 Patient Summaries

Patient 1 (PT 1): PT 1 is a middle-aged female who presented after a motor vehicle collision. The patient had suffered multiple orthopedic injures, a small subarachnoid brain bleed, and an internal carotid artery injury. She remained in the hospital for 12 days and then was discharged to an in-state rehabilitation facility.

Patient 2 (PT 2): PT 2 is a middle-aged male who presented with a single stab wound to the chest with cardiac involvement. A pericardial effusion and an LV heart laceration were identified requiring operative intervention. He experienced cardiac arrest in the operating room and was resuscitated with massive blood transfusion and intra-cardiac defibrillation. Ventricular septal defect (VSD) (shunting) was detected as a direct result of the 12-hour FREE exam (Figure 1). The subject remained in the hospital for 16 days and was then discharged to home without services.

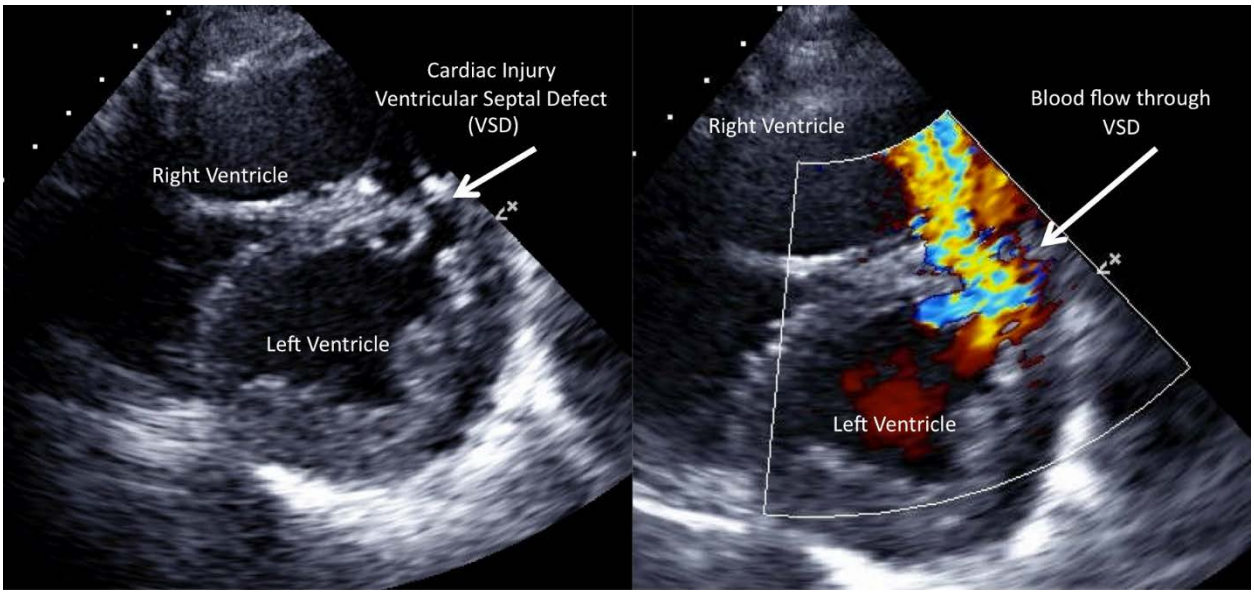

Figure 1. Cardiac injury. *On the left is the para-sternal short axis of the LV; arrow shows injury through the LV septal wall into the RV. On the right is a Doppler image showing pathologic blood flow from the LV to the RV.*

Patient 3 (PT 3): PT 3 is a young man who presented after a motor vehicle collision. Patient suffered multiple orthopedic injuries and pulmonary contusion. Patient underwent multiple orthopedic surgeries for fracture fixation and repair, including a skin flap. He remained in the hospital for 11 days and was then discharged to an in-state rehabilitation facility.

Patient 4 (PT 4): PT 4 is a young man who presented after a fall of approximately 60 feet. He suffered multiple complicated pelvic fractures with associated hematoma. He underwent arterial embolization by interventional radiology. In addition, multiple orthopedic injuries required multiple sessions of operative intervention. The subject remained in the hospital for 30 days before discharge to an in-state rehabilitation facility.

Patient 5 (PT 5): PT 5 is a young man who presented as a pedestrian struck by a truck causing bilateral de-gloving injuries of the lower extremities, multiple complicated pelvic fractures, and pneumothorax. Over the course of a 49-day hospital stay, the patient underwent multiple orthopedic surgeries and experienced persistent hemodynamic instability requiring consistent blood transfusions. He developed bacteremia of Gram-positive cocci originating from catheter lines. This infection was detected on day 8 of his hospital stay and was treated with a course of vancomycin. He was discharged to an in-state rehabilitation facility.

Patient 6 (PT 6): PT 6 is a young man who presented after a motorcycle crash. His injuries included open femur and tibial fractures with vascular involvement (proximal peroneal and mid-anterior tibial arteries). This patient underwent multiple orthopedic surgeries over the course of his 20-day hospital stay. On day 3, Gram-negative rod bacteremia was detected. The Gram-negative rod bacteremia was later identified as *Acinetobacter*, which was treated with a course of Zosyn. He was discharged home without services.

5.2 Outcome

All of the patients survived admission. Mild acute kidney injury was observed in three of six patients. All three exhibited low urine output during the first and second day (hours 36-66), with a mild increase in creatinine at 72 hours (PT 1, 5, 6). None of the patients required renal replacement therapy, and renal function returned to normal in all three. All of the patients required mechanical ventilation, but none met criteria for adult respiratory distress syndrome. The patient sample size is too small to perform any meaningful statistical analysis.

5.3 Echocardiographic Data

5.3.1 Volume Assessment. Half of the patients appeared relatively full at the time 0 FREE, as assessed by the LVIDd, the IVC, and Δ IVC. PT 3, PT 4, and PT 5 still appeared under-filled at the 6-hour time point; it was not until the 18-hour time point that they appeared more volume replete, as evidenced by an IVC > 2 cm or an increase in LVIDd.

All of the patients received over 800 cc of blood product over the first 6-12 hours, with 50% also getting at least 1 liter of crystalloid. The majority of fluid was given to PT 4 and PT 5, who appeared under-filled. However, the highest crystalloid administration was to PT 2, who had a cardiac injury with RV dysfunction and evidence of pressure volume overload, and PT 6, who had a mildly depressed EF. The primary indication for the blood and fluid was hypotension. Taken together this suggests that 40-50% of the time, fluid boluses may not be beneficial. The break of 50% of patients appearing under-filled and 50% appearing replete to even overloaded at 6 hours indicates that if better powered this study could yield a correlation between outcome and echocardiographic findings.

5.3.2 Functional Assessment. Four of six (66%) patients were found to have a mildly depressed EF (50-55%) early in the resuscitative period. PT 4 and PT 6 demonstrated a mildly depressed EF at the time 0 FREE and PT 5 at the 6-hour time point. Both PT 5 and PT 6 intermittently demonstrated dysfunction until the 48-hour time point, at which time the systolic function returned to normal for the remainder of the 72-hour period. Progressively worsening RV dysfunction was found in PT 2; this pre-dated the detection of his VSD.

Diastolic dysfunction was observed on days 0 and 1 in four of six patients (PT 1, 2, 4, 6). Three patients (PT 2, 4, 5) exhibited an intermittently depressed LVEF during the 10-day period. PT 3 exhibited no dysfunction on any of his echocardiograms.

5.4 Biomarker Data

Longitudinal data were obtained on all of the study biomarkers. These included the cardiac biomarkers HS TNI, BNP, and ANP. They also included the endothelial biomarker ADM, the renal biomarker NGAL, and PCT as a measure of inflammation.

5.5 Cardiac Biomarkers

5.5.1 HS TNI. For all of the cardiac biomarkers, PT 2, who sustained a cardiac injury and underwent cardiopulmonary resuscitation, demonstrated massive elevated TNI, BNP, and ANP. Overall, five out of six of the patients demonstrated an early peak in TNI: four patients at 6 hours and one patient at 30 hours. Interestingly, PT 6 demonstrated a peak at 6 and 30 hours (Figure 2). By 72 hours, the TNI in all of the patients had returned to baseline. However, when looking at the 10-day data, a second rise in HS TNI was seen in four of the six patients from days 9-10 (Figure 3).

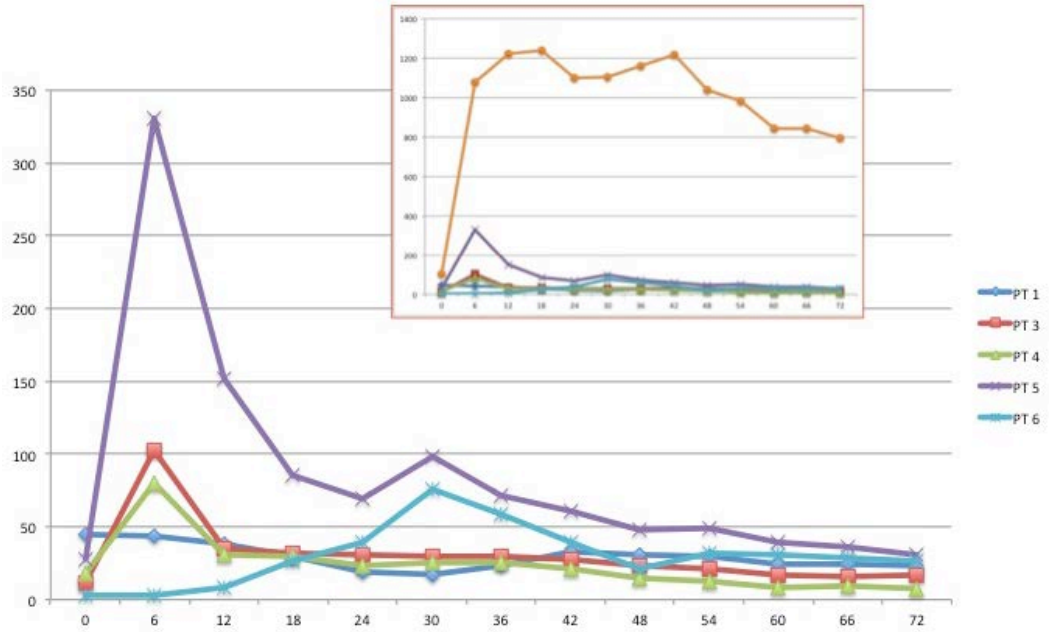

Figure 2. Hourly HS TNI without PT 2. *Upper inset includes PT 2. Note the 6-hour peak.*

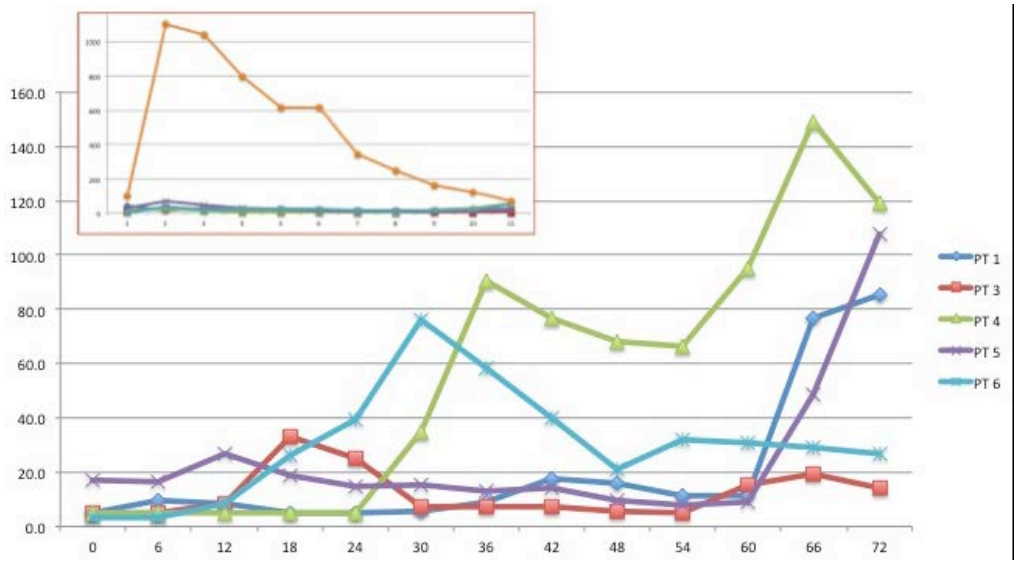

Figure 3. HS TNI daily not including PT 2. *Upper inset includes PT 2. Note the late trend-up in the marker.*

5.5.2 BNP. In three of six patients there was a peak in BNP observed as well, but at a later time point, between 24-36 hours. Unlike with TNI, however, there is a second. Interestingly, BNP appeared to be rising at the 72-hour time point in four of the six patients (Figure 4). When looking out over the 10-day course, all of the patients had one spike in BNP, in-between days 4-9. Interestingly, HS TNI and BNP were both only mildly elevated on admission, suggesting that may be a result of aspects of resuscitation rather than a marker of initial injury. Indeed, the only patient with admission HS TNI above 50 was PT 2, who sustained a cardiac injury.

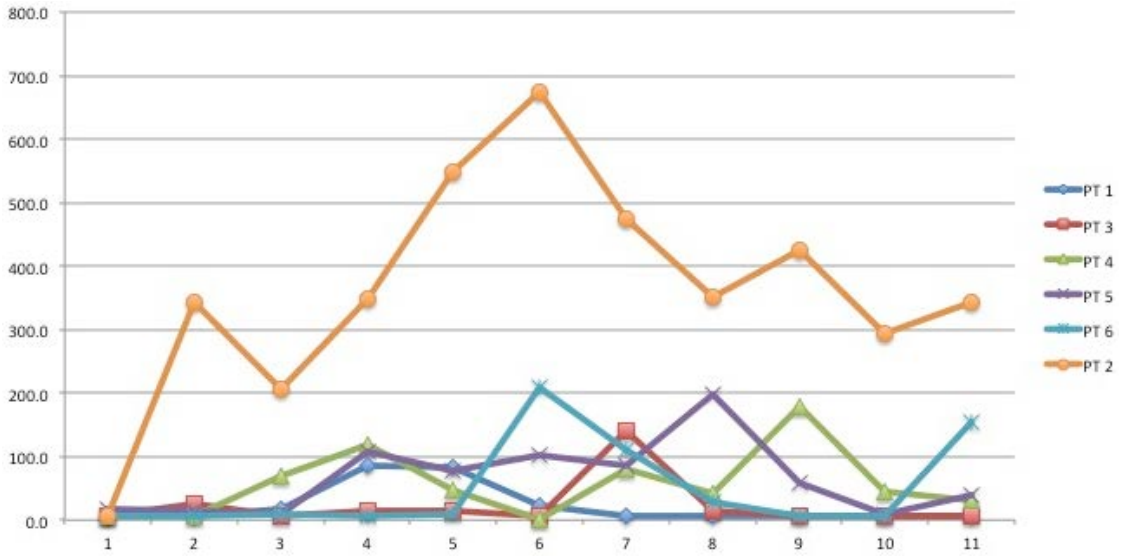

Figure 4. Daily BNP level. *Note the peaks from days 4-9.*

5.5.3 ANP. These data were processed, but appear to be fairly scattered without a clear pattern. We are in the process of analyzing the data further.

5.6 Non-Cardiac Markers

For all of the non-cardiac biomarkers, there is less variability in the initial every 6-hour data points; as a result, only the daily values are discussed.

5.6.1 NGAL. Unlike the cardiac biomarkers, NGAL was initially elevated in all of the patients and trended steadily down in the first 24 hours. In all of the patients, there was a spike observed later in their hospital course; in PT 3 this was observed at day 2, but in the majority of patients it was seen at days 8-9, suggesting possible end-organ dysfunction as a result of the shock period (Figure 5).

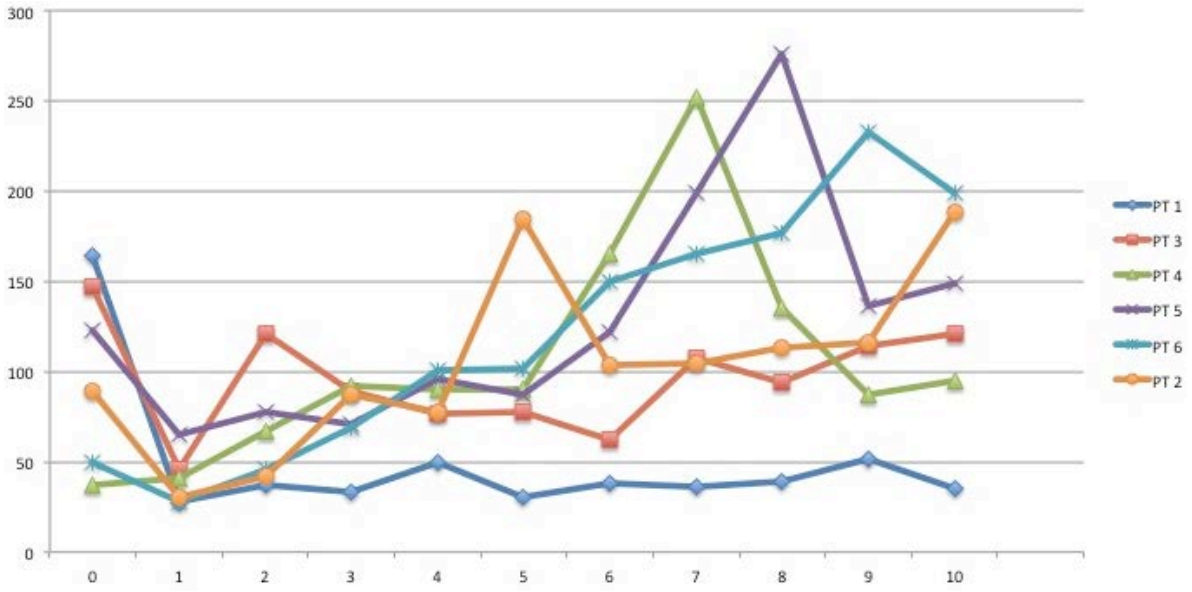

Figure 5. NGAL daily levels. *Note the rise from days 5-9.*

5.6.2 ADM. In five of six patients, the ADM was mildly elevated on admission, but doubled or tripled with a peak at days 1-2. Of note, PT 5 and PT 6, who also developed infections, had a second spike at days 8-9 (Figure 6).

5.6.3 PCT. In the majority of patients, the PCT on admission was close to 0, and the spike to a maximum occurred at day 1, slowly returning to normal by about 7 days.

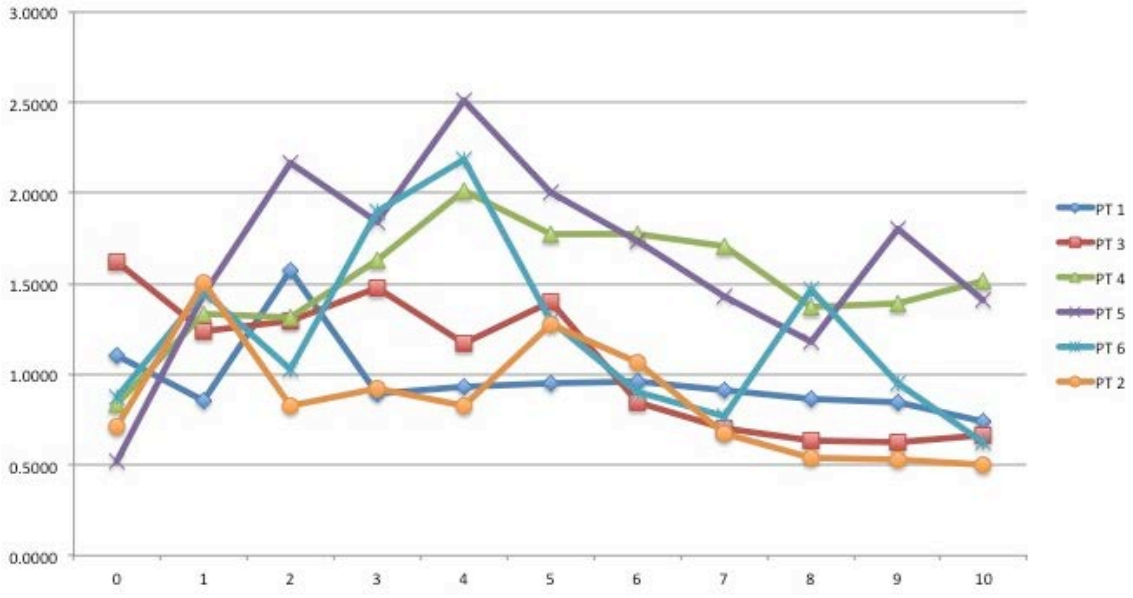

Figure 6. Daily ADM. *Note the peaks at days 2-4.*

6.0 DISCUSSION

This study provides evidence that resuscitation of trauma patients does not end after 24 hours, but is an ongoing process that lasts for several days, with inflammatory mediators and intermittent cardiac dysfunction present for upwards of 10 days. Furthermore, it indicates that even in small study populations of young patients, there is early dysfunction in 50% of patients with traumatic shock, often within 6 hours of presentation. In addition, it provides support for the hypothesis that bedside echo can help guide fluid resuscitation by (1) identifying patients in whom fluid may not be beneficial and (2) diagnosing missed cardiac injuries. Taken together, this has major implications for transportation of the combat injured, as it suggests that the sequelae of severe trauma may last several days, during which time the patient may undergo aeromedical evacuation and is at risk from a variety of complications.

The trend of both the serial echocardiograms and the biomarkers suggests that cardiac dysfunction develops early, within 6 hours of admission, and is followed by evidence of endothelial damage (ADM) from days 2-4 and renal injury (NGAL) from days 7-8. Troponin is released by ischemic myocardium; its early peak combined with dysfunction suggests that sub-clinical low-grade myocardial ischemia occurs early in trauma and could at least be part of the reason for delayed organ dysfunction. It may be that there is a sub-group of young patients with previously normal cardiac function, and likely normal coronary perfusion, who could benefit from a more cardio-protective, fluid-limited method of resuscitation.

In addition to providing insight into fluid management and cardiac function, the data indicate the FREE and HS TNI could serve as valuable tools in detection of cardiac dysfunction and missed cardiac injury. The data also suggest that BNP may not be a useful measure of volume status, as it appears to peak after the initial resuscitation period. Its more delayed presentation suggests it may indicate post-resuscitation phase shock, when the massive fluid resuscitation of early shock returns to the vascular space as the inflammatory process abates. This may be leading to atrial stretch, causing BNP to be released.

Other than the feasibility of the study, and the utility of echocardiography, no definitive conclusions can be drawn from this very small study. However, the data indicate that further study in this area is very likely to lead to important discoveries that could improve the care of the combat injured during evacuation and transport.

7.0 CONCLUSIONS

7.1 Military Relevance

- A civilian trauma can be used to create a reasonable model of the combat injured, provided the inclusion criteria represent the military.
- The FREE could be used in a variety of assessment and transport scenarios to determine who is safe to transport and to manage patients who decompensate in flight.
- With further validation in a greater number of patients, HS TNI may prove to be a method of identifying patients at risk for dysfunction or who have cardiac injury.

7.2 Clinical Indications

- The FREE is an established tool that can be used to diagnose cardiac injury and manage fluid in trauma patients.
- It is possible that there is a sub-group of young trauma patients who may benefit from a more fluid-limited, cardio-protective method of resuscitation.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADM	mid-regional pro-adrenomedullin
ANP	mid-regional pro-atrial natriuretic peptide
BNP	B-type natriuretic peptide
EF	ejection fraction
FREE	focused rapid echocardiographic evaluation
HS TNI	high sensitivity cardiac troponin I
ICU	intensive care unit
IVC	inferior vena cava
IVCd	inferior vena cava diameter
Δ IVC	change in inferior vena cava diameter with respiration
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
LVIDd	left ventricular internal dimension at end diastole
NGAL	neutrophil gelatinase-associated lipocalin
PAC	pulmonary artery catheter
PCT	procalcitonin
PT1	patient one
PT2	patient two
PT3	patient three
PT4	patient four
PT5	patient five
PT6	patient six
RV	right ventricle/ventricular
VSD	ventricular septal defect